1238597

PATENT SPECIFICATION

(11) 1238597

NO DRAWINGS

(21) Application No. 29884/69 (22) Filed 12 June 1969

(31) Convention Application No. 737 365 (32) Filed 17 June 1968 in

(33) United States of America (US)

(45) Complete Specification published 7 July 1971

(51) International Classification C 08 g 49/00; A 61 k 27/00

(52) Index at acceptance

C3R 35C16 35C17X 35C21 35C25 35C29 35C4 35D3 35L1B 35L2CX 35L2X 35P1A 35P2 35PX 35T2

A5B 26Y 351 352 35Y 382 38Y

(54) HYPERCHOLESTEREMIA LOWERING AGENT

(71) We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to compositions and processes for combatting and reducing hypercholesteremia in affected mammals, for example, dogs and birds such as chickens by orally administering thereto an effective amount of a non-toxic polymer prepared from (1) a polyethyleneimine and a bifunctional substance e.g. epichlorohydrin or 1,2:3,4-diepoxybutane or (2) a polyethyleneimine and an epoxide e.g. epoxythane (ethylene oxide) or 2,3-epoxy-1-propanol(glycidol).

In accordance with the manner and process of using the present invention, a sufficient amount of a cholesterol-lowering agent is orally administered to the affected mammals and birds to provide beneficial effects in lowering cholesterol. The cholesterol-lowering agent is administered after compounding into dosage forms with a nontoxic, compatible, edible oral carrier. The polyethyleneimines used in providing the polymers are of the formula

$$NH_2—(CH_2CH_2NH)_n—H$$

where n is a number from 4 to 1000. They have the low equivalent weight of approximately 43. From among these polyethyleneimines tetraethylenepentamine and a polyethyleneimine having a viscosity of about 15,000 cps. (when anhydrous) are preferred. Polyethyleneimines are described in U. S. Patents 2,644,760; 3,152,188; 3,308,020; and 3,332,841. Sources of polyethyleneimines are the Dow Chemical Company and the Industrial Chemical and Dye Company.

In order to provide copolymers of the inventive process, such polyethyleneimines are cross-linked with certain bifunctional compounds having epoxy groups and/or halogen atoms; namely, epichlorohydrin, glycerol-1,3-dichlorohydrin, 1,2:3,4-diepoxybutane, bis-epoxypropyl ether, ethylene glycol bis-epoxypropyl ether and 1,4-butanediol bis-epoxypropyl ether according to known methods; for example, those of U. S. Patent 3,002,823; Peterson and Sober, J. Am. Chem. Soc. *78*:751-755 (1956), and McKernan and Ricketts, Chemistry and Industry, November 21 (1959) pgs. 1490-1491. Illustratively, with epichlorohydrin as cross-linking agent the copolymer contains cross-links represented by

$$—CH_2CHOHCH_2—;$$

with 1,2:3,4-diepoxybutane by

$$—CH_2CHOHCHOHCH_2—;$$

with bis-epoxypropyl ether by

$$—CH_2CHOHCH_2OCH_2CHOHCH_2—.$$

Likewise with ethylene glycol bis-epoxypropyl ether the copolymer contains cross-links represented by

$$—CH_2CHOHCH_2OCH_2\ CH_2OCH_2CHOHCH—,$$

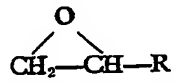
and in the case of 1,4-butanediol bis-epoxy-propyl ether by

$$—CH_2CHOCH_2O(CH_2)_4OCH_2CHOHCH_2—.$$

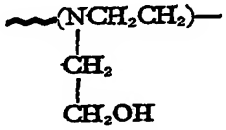
AQ5

Hence, these copolymer cross-linked products contain a residue of an aliphatic radical having three to ten carbon atoms inclusive. The content of cross linking moiety expressed as % by weight of the polymer is at least 10%, preferably at least 14%, and reaches in some cases 47% or higher.

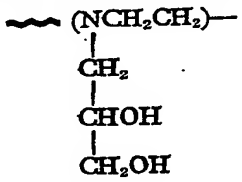
Further, the process of the present invention utilizes graft polymers of the polyethyleneimines and an epoxide of the formula:



wherein R is hydrogen, hydroxymethyl, lower alkyl having one to six carbon atoms inclusive; for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl; or phenyl. Examples of such epoxides are: epoxyethane (ethylene oxide), 2,3-epoxy-1-propanol (glycidol), 1,2-epoxypropane, 1,2-epoxybutane, 1,2-epoxypentane, 1,2-epoxyhexane and styrene oxide (phenylethylene oxide). Illustratively, the substituted nitrogens of the graft polymers of polyethyleneimine with ethylene oxide can be represented by the formula:



and with glycidol by the formula:



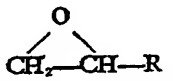
The polymer suitably prepared as required or desired with an edible oral carrier into an oral dosage form is administered in varying amounts depending upon the weight of the mammals and birds under treatment. The preferred regimen of the oral administration is four times daily. Each dosage amount ranges from about 0.5 Gm. to about 25 Gm., preferably from about 2.5 Gm. to about 3.75 Gm. Suitably the active ingredient can be reduced to a particle size of no more than about 50 microns. Both the free base and acid addition salt forms of the polymers are operable, for example, the hydrochloride, sulfate, phosphate and citrate. Oral administration of the polymers provides a method of binding bile acids and combatting hypercholesteremia which is free of the unsatisfactory and unacceptable taste and/or odour which usually accompany methods utilizing, for example, too oily vehicles or quaternary ammonium ion exchangers based on polystyrenes with divinylbenzene moieties.

The term "edible oral carrier" means the diluents, excipients, aqueous vehicles, oily vehicles, binders, disintegrators, and lubricants used by those skilled in the art in preparing oral dosage forms and products, e.g. capsules, gels, magmas, powders, solutions, emulsions, suspensions, granules, and tablets. It also means animal and bird rations containing the usual dietary ingredients, that is, carbohydrate, fat, mineral, proteins and vitamins; for example, the diet for cockerels, Tenant et al., Proc. Soc. Exp. Biol. Med. *96*: 679 (1957) and similar rations for dogs.

Also according to the invention there are provided novel pharmaceutical compositions comprising a non-toxic ingestible polymeric reaction product of a polyethyleneimine of the formula

$$NH_2—(CH_2CH_2NH)_n—H$$

wherein n is a number from 4 to 1,000, and epichlorohydrin, glycerol-1,3-dichlorohydrin, 1,2: 3,4-diepoxybutane, bis-epoxypropyl ether, ethylene glycol bis-epoxypropyl ether, 1,4-butanediol bis-epoxypropyl ether, or an epoxide of the formula:



wherein R is hydrogen, hydroxymethyl, lower alkyl having from 1 to 6 carbon atoms inclusive or phenyl, or an acid addition salt of said reaction product other than a composition that is a non-sterile aqueous solution or an unflavoured solution.

Additional active ingredients, while not necessary to the embodiments of the inventive concept, can suitably be added thereto, for example, unsaturated fatty acids e.g. linoleic acid, arachidonic acid and linolenic acid; edible vegetable oils e.g. as corn oil and safflower oil; choleretic agents e.g. as tocamphyl and florantyrone; fecal softeners e.g. as poloxalkol and dioctyl sodium sulfosuccinate; other hypocholesteremic agents e.g. the D-isomer of 3,3',5-triiodothyronine, triiodothyropropionic acid; thyroxine compounds e.g. sodium L-thyroxine and sodium D-thyroxine; nicotinic acid, clofibrate, nafoxidine hydrochloride, 5-methylpyrazole-3-carboxylic acid and 3-methyl-5-isoxazolecarboxylic acid.

Preparation 1

To a cold solution of 38 Gm. (0.20 mole) of tetraethylenepentamine and 400 ml. of water under a nitrogen atmosphere is added with stirring 39 ml. (46.2 Gm., 0.50 mole) of epichlorohydrin. The mixture is stirred at room temperature overnight, then heated on a steam bath for 2.5 hours. The mixture (pH ca. 6) is cooled and the pH of the solution is adjusted to 4.0 with concentrated hydrochloric acid.

The resulting solution is then dialyzed for 17 hours using cellulose casing (Union Carbide Corp.). Isolation of the product by freeze-drying gives 32 Gm. of copolymer hydrochloride. The dried copolymer has a low solubility in water, but swells in contact with water. Content of cross-linking moiety is about 44%.

Anal. Found: C, 44.59; H, 8.02; Cl, 20.73; N, 14.61.

Preparation 2

In another preparation, 114 Gm. of tetraethylenepentamine in 1000 ml. of water is treated with 117 ml. of epichlorohydrin at ambient temperature for 1 hour and at 95°C. for 3.5 hours. The pH of the cooled mixture is adjusted to 4—4.5 with 24 ml. of concentrated hydrochloric acid and after concentration of the dialyzed solution there is obtained 250 Gm. of copolymer solution containing 49.4% copolymer by weight.

Preparation 3

Heat is applied carefully to a mixture of 38 Gm. of tetraethylenepentamine, 400 ml. of water and 19 ml. of epichlorohydrin until the exothermic reaction subsides. An additional 19 ml. of epichlorohydrin is added dropwise and the resulting mixture is heated and stirred at 60°C. for 2 hours. The mixture is cooled and basified to pH 8.5 using concentrated aqueous potassium hydroxide solution, then heated again for 1 hour. The mixture is cooled, basified to pH 11 with aqueous potassium hydroxide solution and then dialyzed in cellulose casings for 1.5 days. The resulting solution is acidified to pH 6 with concentrated hydrochloric acid. The mixture is concentrated on a rotating evaporator and the resulting residue is dried *in vacuo* at 70°C. The product is pulverized in a Waring Blendor, yield 51 Gm. This material swells in the presence of water but does not dissolve.

Preparation 4

A mixture of tetraethylenepentamine and epichlorohydrin is polymerized in water solution as in Preparation 3. The pH of the mixture is adjusted to 12 with aqueous potassium hydroxide solution and the resulting solution is dialyzed as described above. To provide an acid addition salt, the pH of an aliquot of the aqueous solution of the copolymer is adjusted to a pH of about 7 with sulfuric acid. Other such acids can also be used, for example, phosphoric acid and citric acid. The products are isolated in the usual way. Both the free base and acid addition salt forms are useful as embodiments of the invention to provide hypocholesteremic effects.

Preparation 5

To a mixture of 246 Gm. of an aqueous solution of polyethyleneimine, viscosity about 15,000 cps. (when anhydrous), Industrial Chemical and Dye Co., Inc., containing 82 Gm. of polymer, and 750 ml. of water is added 19.5 ml. of epichlorohydrin with stirring. The gelatinous mixture is heated at 70°C. for 2 hours before being dispersed with a Waring Blendor. The mixture is again heated at 70°C. for 2 hours and then let stand overnight at room temperature. The mixture is partially neutralized with 100 ml. of concentrated hydrochloric acid and diluted to a weight of 1490 Gm. with water. The resulting aqueous preparation contains approximately 10% copolymer by weight. The content of cross-linking moiety is about 14%.

Preparation 6

To a solution of 189 Gm. (1 mole) of tetraethylenepentamine in 1500 ml. of water is added 2 moles of 1,2:3,4-diepoxybutane in portions so as to control the exothermic reaction. The solution is then heated at 80—100°C. for 2—5 hours. The mixture is cooled and dialyzed to remove unwanted low molecular weight material. The aqueous solution is adjusted to pH about 7 with hydrochloric acid to prepare the copolymer hydrochloride.

Preparation 7

In a like manner to Preparation 6, the tetraethylenepentamine is replaced with an equivalent weight of pentaethylenehexamine and the latter is copolymerized with 2.5 moles of 1,2:3,4-diepoxybutane to give the corresponding copolymer.

Preparation 8

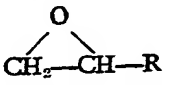
A solution of 76 Gm. of tetraethylenepentamine, 800 ml. of water and 39 ml. of epichlorohydrin is stirred at ambient temperature for one hour and at 90°C. for an additional hour, then cooled to 30—40°C. Sodium hydroxide (15 Gm.) in 30 ml. of water is added followed by 39 ml. of epichlorohydrin. The mixture is again stirred at ambient temperature for one hour and at 90°C. for one hour when 15 Gm. of sodium hydroxide in 30 ml. of water is added. The mixture is heated on the steam bath for 2 hours to produce a thick jelly. The pH of the mixture is adjusted to 6 with concentrated hydrochloric acid and the copolymer hydrochloride is precipitated using ethanol. The rubbery product is triturated with ethanol (2 times), dried *in vacuo* at 80°C. and the resulting solid is ground to a fine powder using a Waring Blendor, yield 110 Gm.

Preparation 9

To a warm solution of 3.78 kg. (20 moles) of tetraethylenepentamine in 40 l. of water is added 4.6 kg. (50 moles) of epichlorohydrin. After the exothermic reaction subsides (about one hour), 4 kg. of 50% aqueous sodium hydroxide solution (50 moles) is added. The resulting neutralized gel is transferred to flat trays and air-dried at 80°C. The dry solid is suspended in water, the suspension is filtered, and the filter cake washed with water. The cake is air-dried at 80°C. to 6.8 kg. of

copolymer which is then milled to produce a uniform granular solid suitable for use in formulation.

Generally, the manner of making the polymers of polyethyleneimine and the epoxides of the above formula:



where R is as defined above, is to start with an aqueous solution of polyethyleneimine. To 100 to 300 ml. of such an aqueous solution containing about 42 Gm. of the polyethyleneimine is added with stirring 0.1 to 1 mole of the epoxide in portions so as to control the exothermic reaction. After the initial exothermic reaction subsides, the mixture is heated at 50—100°C. for 0.5 to 5 hours. The mixture is cooled and dialyzed if desired to remove superfluous low molecular weight material. The polymer solution is then acidified with a suitable acid until the solution reaches a suitable pH and the solution is then concentrated if desired (or diluted). Suitable acids include hydrochloric, hydrobromic, sulphuric, acetic, nicotinic and phosphoric. Suitable pH's are from about 2 to 9. The concentration step can be carried to the point of obtaining the product as an aqueous solution or as a solid which can be ground or pulverized and formulated. In the case of insoluble epoxides, it is advantageous to carry out the polymerization in ethanolic or aqueous-ethanolic solution and to then remove the ethanol in the concentration step.

Preparation 10

To a mixture of 123 Gm. of aqueous polyethyleneimine solution (containing 41 Gm. of polymer) and 250 ml. of water is added 37 Gm. of glycidol. The mixture (exothermic) is stirred at ambient temperature overnight and is then heated at 85—90°C. for 2 hours. The cooled mixture is dialyzed in cellulose casings for 3 days giving the polymer (pH of solution, 11.5). The mixture is acidified to pH 5 with concentrated hydrochloric acid (ca. 70 ml.) and concentrated *in vacuo* to give 254 Gm. of an aqueous solution containing 36% polymer hydrochloride. The polymer is obtained as a water-soluble solid by removing the remaining water.

Preparation 11

To 200 ml. of an aqueous solution of polyethyleneimine (containing 41 Gm. of polymer) in a glass-lined steel bomb at about 0°C. is added 50 ml. of cold ethylene oxide. The bomb is sealed and the mixture is shaken at ambient temperature for several hours and then at 100°C. for 4—5 hours. The mixture is cooled and then dialyzed in cellulose casings for 24 hours to give the polymer (pH of solution 12). The mixture is acidified to pH 5 with concentrated hydrochloric acid and is then concentrated *in vacuo* to give 233 Gm. of an aqueous solution containing 43% polymer hydrochloride.

Materials and methods for evaluating the novel process of this invention are described by Parkinson, J. of Lipid Research, *8*: 24-29 (1967). Therein, for example, bile acid-binding capacity can be determined by adding a weighed amount of a polymer to a 1% solution of bile acid in 0.9% saline at pH 6.2. The mixture is well shaken, centrifuged and the supernatant separated for determination of cholic acid. Decreases in the cholic acid content show effective bile acid-binding capacity. Likewise, cockerels made hypercholesterodemic by a diet to which 2% of cholesterol is added are used to determine serum sterol lowering effects when the diet is supplemented with known amounts of the active polymers.

The following exemplifications illustrate the method of using the invention and also include therein illustrations of some novel pharmaceutical formulations.

EXAMPLE 1 Effect of Tetraethylenepentamine-Epichlorohydrin Copolymer Hydrochloride in Cholesterol-Fed Cockerels.

Regimen	Weight Gain (Gm./Bird)	Food Intake (Gm./Bird)	Wt. Gain / Food Intake	Serum Sterols (mg./100 ml.)
Basal Diet	86	176	.49	146*
+2% Cholesterol	87	195	.45	307
+0.5% Copolymer (143A)	85	183	.46	197
+0.05% Copolymer (142A)	—	—	—	242**
+0.5% Copolymer (142B)	91	205	.44	283
+1% Copolymer (143A)	91	186	.49	140
+1% Copolymer (142A)	85	179	.47	166
+1% Copolymer (142B)	83	187	.44	219
+3% Copolymer (143A)	84	171	.49	113
+3% Copolymer (142A)	73	151	.48	130
+3% Copolymer (142B)	80	190	.42	126

* 6 birds/group in all groups except **

** 5 birds/group

(143A) Copolymer (Preparation 8) used as hydrochloride powder.

(142A) Copolymer (Preparation 1) used as 50% of hydrochloride in water

(142B) Copolymer (Preparation 1) used as hydrochloride powder.

EXAMPLE 2 Capsule

One thousand two-piece hard gelatin capsules for oral use, each containing 500 mg. of tetraethylenepentamine - epichlorohydrin copolymer (Preparation 1) are prepared from the following ingredients:

Tetraethylenepentamine-epichlorohydrin copolymer	500 Gm.
Talc, U.S.P.	50 Gm.
Magnesium stearate, U.S.P.	2 Gm.

The finely powdered ingredients are mixed thoroughly, then filled into hard gelatin capsules of appropriate size.

Two capsules are taken four times a day with meals and an evening snack to lower blood cholesterol in hypercholesteremic patients.

EXAMPLE 3 Powder packets

Ten thousand powder packets, each containing 3.75 Gm. of a tetraethylenepentamine-epichlorohydrin copolymer (Preparation 9), are prepared from the following:

Tetraethylenepentamine-epichlorohydrin copolymer	37,500 Gm.

One or two packets emptied and stirred into water, fruit or vegetable juices, skimmed milk, or mixed with cereal, applesauce or other food, is given three times daily with meals in the relief of severe pruritis associated with bile stasis such as in biliary cirrhosis with incomplete ciliary obstruction.

EXAMPLE 4 Oil Suspension

One thousand ml. of an oral suspension containing 750 mg. of tetraethylenepentamine-diepoxybutane copolymer (dry powder) in each 5 ml. is prepared from the following ingredients:

Tetraethylenepentamine-diepoxybutane copolymer	150 Gm.
Oil base, q.s.	1,000 ml.

The oil base consists of equal parts of soybean oil and purified linseed oil gelled with 1% aluminium monostearate. Each 5 ml. of

base supplies 1.1 ml. of linolenic acid. One or two teaspoonfuls (5 or 10 ml.) administered three times a day with meals is useful in the treatment of atherosclerosis.

EXAMPLE 5 Aqueous Suspension

An aqueous oral suspension, containing in each tablespoon (10 ml.) 1,000 mg. of a polyethyleneimine - epichlorohydrin copolymer (Preparation 5), is prepared from the following materials:

Polyethyleneimine-epichlorohydrin copolymer	1,000 Gm.
Pectin, N.G.	100 Gm.
Deionized water, q.s.	10,000 ml.

One tablespoon (10 ml.) is given three times a day, with meals, to lower blood cholesterol in hypercholesteremic individuals.

EXAMPLE 6 Powder Packets

Five thousand powder packets, each containing 25 Gm. of polyethyleneimine-glycidol graft polymer, are prepared from 125,000 Gm. of the polymer (Preparation 10).

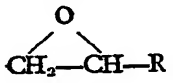
One packet emptied and stirred into water, non-caloric fruit or vegetable juice or skimmed milk, is taken four times daily to reduce the serum sterol levels in hypercholesteremic patients.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising a non-toxic ingestible polymeric reaction product of a polyethyleneimine of the formula

$$NH_2—(CH_2CH_2NH)_n—H$$

wherein n is a number from 4 to 1,000, and epichlorohydrin, glycerol-1,3-dichlorohydrin, 1,2:3,4-diepoxybutane, bis-epoxypropyl ether, ethylene glycol bis-epoxypropyl ether, 1,4-butanediol bis-epoxypropyl ether, or an epoxide of the formula:



wherein R is hydrogen, hydroxymethyl, lower alkyl having from 1 to 6 carbon atoms inclusive or phenyl, or an acid addition salt of said reaction product other than a composition that is a non-sterile aqueous solution or an unflavoured solution.

2. A pharmaceutical composition in the form of capsules containing the reaction product as defined in claim 1.

3. A pharmaceutical composition in the form of hard gelatin capsules containing the reaction product as defined in claim 1 that is in the form of a hydrochloride powder.

4. A pharmaceutical composition in the form of a powder containing the reaction product as defined in claim 1 together with a food composition.

5. A pharmaceutical composition in the form of an oil suspension containing the reaction product as defined in claim 1 together with an oil base.

6. A pharmaceutical composition as claimed in claim 5 in which the oil base is soya bean oil and linseed oil.

7. A pharmaceutical composition in the form of an aqueous suspension containing a reaction product as defined in claim 1.

8. A pharmaceutical composition in the form of an aqueous suspension as claimed in claim 7 together with pectin and deionised water.

9. A pharmaceutical composition for administration to mammals other than humans comprising the reaction product as defined in claim 1 together with at least one edible solid dietary constituent.

10. A pharmaceutical composition according to any preceding claim in which the reaction product is tetraethylenepentamine epichlorohydrin copolymer.

11. A pharmaceutical composition as claimed in any of claims 1 to 9 in which the reaction product is tetraethylenepentamine 1,2:3,4-diepoxybutane copolymer.

12. A pharmaceutical composition as claimed in any of claims 1 to 9 in which the reaction product is a polyethyleneimine glycidol copolymer.

13. A pharmaceutical composition as claimed in any of claims 1 to 9 in which the reaction product is pentaethylenehexamine 1,2:3,4-diepoxybutane.

14. A pharmaceutical composition as claimed in any of claims 1 to 9 in which the reaction product is a polyethyleneimine ethylene oxide copolymer.

15. A pharmaceutical composition according to any preceding claim additionally comprising an unsaturated fatty acid.

16. A pharmaceutical composition as claimed in claim 15, in which the unsaturated fatty acid is linoleic acid, arachidonic acid or linolenic acid.

17. A pharmaceutical composition as claimed in any of the preceding claims additionally comprising an edible vegetable oil.

18. A pharmaceutical composition as claimed in claim 17 in which the edible vegetable oil is corn oil or safflower oil.

19. A pharmaceutical composition as claimed in any of the preceding claims additionally comprising a choleretic agent.

20. A pharmaceutical composition as claimed in claim 19 in which the choleretic agent is tocamphyl or florantyrone.

21. A pharmaceutical composition as claimed in any preceding claim additionally comprising fecal softeners.

22. A pharmaceutical composition as claimed in claim 20 in which the fecal softener is poloxalkol or dioctyl sodium sulphosuccinate.

23. A pharmaceutical composition as

claimed in any preceding claim additionally comprising a hypocholesteremic agent other than the reaction product defined in claim 1.

24. A pharmaceutical composition as claimed in claim 23 in which the additional hypocholesteremic agent is the D-isomer of 3,3',5-triiodotyronine, or triiodothyropropionic acid.

25. A pharmaceutical composition as claimed in any preceding claim additionally comprising a thyroxine compound.

26. A pharmaceutical composition as claimed in claim 25 in which the thyroxine compound is sodium-L-thyroxine or sodium D-thyroxine.

27. A pharmaceutical composition as claimed in any preceding claim additionally comprising nicotinic acid.

28. A pharmaceutical composition as claimed in any preceding claim additionally comprising clofibrate.

29. A pharmaceutical composition as claimed in any preceding claims additionally comprising nafoxidine hydrochloride.

30. A pharmaceutical composition as claimed in any preceding claim additionally comprising 5-methylpyrazole-3-carboxylic acid.

31. A pharmaceutical composition as claimed in any preceding claim additionally comprising 3 - methyl - 5 - isoxazolecarboxylic acid.

32. A unit dosage of pharmaceutical composition in which the dose comprises 0.5 grams to 25 grams of a reaction product defined in claim 1 together with a compatible edible oral carrier.

33. A pharmaceutical composition as claimed in any of claims 1 to 32 substantially as herein described with reference to the Examples.

34. A method of lowering hypercholesterolemia in mammals excluding humans by administering a pharmaceutical composition substantially as herein described with reference to the Examples.

For the Applicants:—
GILL, JENNINGS & EVERY,
Chartered Patent Agents,
51 & 52 Chancery Lane,
London, W.C.2.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1971.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.